to IL-1, mitogenesis by itself is not indicative of an anabolic response. Mitogenesis of cultured articular chondrocytes is almost always accompanied by the loss of production of the matrix proteins that comprise the hyaline cartilage matrix, specifically sulfated proteoglycans and type II collagen, and production of these matrix proteins is important in achieving repair of a degenerating joint. Studer et al. included proteoglycan synthesis in their analysis and demonstrated that the combination of IGF-1 and the iNOS inhibitor L-NMA (O01735) or the combination of TGF-β and the COX-2 inhibitor SC-58125 (O01734) stimulated proteoglycan synthesis while the individual agents had little to no effect on their own. In addition, Studer et al. (O01734) examined the effect of various combinations on the expression of TIMP-1, a factor which has positive effects on matrix homeostasis by inhibiting the matrix metalloproteinases and whose expression is suppressed by IL-1. The combination of TGF-β and the p38 MAPK inhibtor SB-203580 induced TIMP-1 expression in IL-1 activated chondrocytes to a level that was greater than the additive effects of both agents alone and greater than that observed in the control cultures that were not treated with IL-1. Increased levels of TIMP-1 should help restore the imbalance in matrix homeostasis that is the primary pathological feature of the osteoarthritic joint. Therefore, the research described in the combined publications of Studer et al. (Reference numbers 001735, 001733, 001734) constitute the first demonstration of which applicant is aware that *a combination of a catabolic inhibitor and an anabolic growth factor that has a greater positive effect on matrix homeostasis than either agent alone.*

In further support of the non-obviousness of the present invention, Applicants also direct the Examiner's attention to an additional non-prior art reference O01697 (Haupt et al, *J Orthopaedic Research* 23: 118-126, 2005) cited in the supplemental IDS submitted with the response on January 3, 2006. The study reported in this paper evaluated the potential of gene induced synoviocyte expression of a combination of AdIGF-1 and AdIL-1Ra to control articular

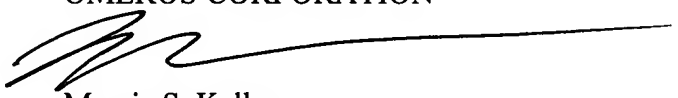
OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

cartilage degradation in explants exposed to IL-1. While the chondroprotective effect of IL-1Ra has been well documented, it is interesting to note that in these IL-1 activated chondrocytes the "combination of IGF-1 and IL-1Ra not only preserved matrix proteoglycan content but stimulated an increase in proteoglycan synthesis to *levels tending higher than normal cartilage*." (Haupt et al. at 124, emphasis added) This surprising effect of a combination of an anabolic promoting agent and a catabolic inhibitory agent can be observed in Figures 3 and 4 of Haupt et al., comparing cartilage explant proteglycan content and DNA content of untransduced cells cultured in normal medium to AdIGF-1/AdIL-1RA induced cells cultured in IL-1β medium. The authors conclude that such therapy "combining an anabolic growth factor to stimulate matrix synthesis and catabolic blockers to prevent matrix degradation by IL-1, protects and partially restores cartilage matrix." (Haupt et al. at 125) The recent literature discussed above thus strongly supports the approach of combining an anabolic promoting agent and a catabolic inhibitory agent, which in accordance with the present claimed invention is delivered locally to the joint.

Applicants respectfully submit that the application be reconsidered and that all claims be passed to issue.

Respectfully Submitted,

OMEROS CORPORATION



Marcia S. Kelbon
Vice President, Patent & General Counsel
Registration No. 34,358
Direct Dial No. 206.676.5020

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688

I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

2-3-06
Date

SJM
Stephanie Jansen

MSK:sj

OMEROS CORPORATION
1420 Fifth Avenue
Suite 2600
Seattle, Washington 98101
206.623.4688